REMARKS

It is respectfully requested that this application be reconsidered in view of the above amendments and the following remarks and that all of the claims remaining be allowed.

Claim Amendments

Claim1 has been amended to recite "cells of the tumor" instead of "tumor cells" for additional clarity. Claim 7 has been amended to delete certain members of a Markush group in order to expedite prosecution of the application.

No new matter has been added by these amendments. The Examiner is hereby requested to enter these amendments.

Applicants submit that all claim amendments presented herein or previously are made solely in the interest of expediting allowance of the claims and should not be interpreted as acquiescence to any rejections or ground of unpatentability. Applicants reserve the right to file at least one continuing application to pursue any subject matter that is canceled or removed from prosecution due to the amendments.

Rejections Under 35 U.S.C. §112, Enablement (Paragraphs 5 and 6 of the Office Action)

The rejection of claims 1-21 under 35 U.S.C. §112, first paragraph, as allegedly not being enabled, is respectfully traversed for the reasons set forth below.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. MPEP §2164.01; *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

Claim 1, as amended, is directed to a method for delivering a virus to a solid tumor to reduce growth of the tumor, comprising administering an effective amount of virus to a subject bearing the tumor, wherein the virus is capable of selectively killing cells of the tumor, by a base

administration of injecting on the same day a composition comprising the virus into multiple sites inside the solid tumor, wherein the volume of the composition injected per site is between about 10% to about 100% of the volume of the tumor. The Office Action takes the position that the specification is enabling for certain embodiments of the claimed method, wherein the virus is reovirus and the solid tumor has an activated Ras pathway (page 3 of the Office Action). The Office Action alleges, however, that the specification does not reasonably provide enablement for the full scope encompassed by the claims, such as solid tumors that do not have an activated Ras signaling pathway. Applicants disagree. To demonstrate that the claimed invention is enabled to the full scope, the *Wands* factors are discussed below in response to the *Wands* analysis of the Office Action.

Nature of the invention

Applicants agree with the Office Action that the invention pertains to viral therapy of tumors.

Breath of the claims

The Office Action states that the claims encompass the administration of any type of virus which is capable of selectively killing tumor cells to any type of solid tumor. Claim 1 has been amended to clarify that the claims encompass the administration of any type of virus which is capable of selectively killing tumors to a solid tumor that can be killed by the virus.

State of the art and predictability

Oncolytic viruses were known in the art at the time the present application was filed. The Office Action states on page 4,

> There does not appear to be any indication in the prior art indicating that any virus other than the reovirus is a[sic] capable of selectively killing tumor cells.

To the contrary, the present specification and the prior art, including the references cited by the Examiner in the Office Action, provide ample examples of such viruses. For example, the specification describes more than ten such viruses at pages 14-19, along with citations of a number of references, such as:

Bar-Eli, N., et al., "preferential cytotoxic effect of Newcastle disease virus on lymphoma cells", J. Cancer Res. Clin. Oncol. 122: 409-415 (1996).

Bischoff J R. et al., "An Adenovirus Mutant that Replicates Selectively in p53-Deficient Human Tumor", Science 274(5286):373-6 (1996).

Blagoslelonny, M. V., et al., "in vitro Evaluation of a p53-Expressing Adenovirus as an Anti-Cancer Drug", Int. J. Cancer 67(3):386-392 (1996).

Fueyo, J., et al., "A Mutant Oncolytic Adenovirus Targeting the Rb Pathway Produces Anti-Glioma Effect in Vivo", Oncogene 19(1):2-12 (2000).

Heise, C. et al., "Replication-selective adenoviruses as oncolytic agents", J. Clin. Invest. 105(7):847-51 (2000).

Nemunaitis, "Oncolytic viruses", J. Invest. New Drugs 17:375-386 (1999).

Reichard, K. W., et al., "Newcastle Disease Virus Selectively Kills Human Tumor Cells", J. of Surgical Research 52:448-453 (1992).

Stojdl, D. F., et al., "Exploiting Tumor-Specific Defects in the Interferon Pathway with a Previously Unknown Oncolytic Virus", Nat. Med. 6(7):821-825 (2000).

Yoon, S. S., et al., "An Oncolytic Herpes Simplex Virus Type I Selectively Destroys Diffuse Liver Metastases from Colon Carcinoma", FASEB J. 14:301-311(2000).

Zorn, U. et al., "Induction of Cytokines and Cytotoxicity against Tumor Cells by Newcastle Disease Virus", Cancer Biotherapy 9(3):22-235 (1994).

These references are all of record, and each of them describes at least one virus, other than reovirus, that can selectively kill tumor cells.

In addition, the Office Action cites Kooby *et al.* (FASEB Journal 13:1325-1334, 1999), which teach viral thrapy using G207. In an area apparently highlighted by the Examiner, Kooby *et al.* teach:

> G207 is a second-generation, multi-mutated, replication-competent herpes cimplex virus type-1 (HSV-1), which has demonstrated impressive oncolytic activity in several neurological malignancies, while sparing normal neural tissue. (page 1325, last line to page 1326, first four lines)

Clearly, G207 can selectively kill tumor cells, and it is not a reovirus.

In view of the above, viruses that can selectively kill tumor cells, other than reovirus, are well known in the art. Furthermore, there does not appear to be any teachings in the art indicating that such viruses cannot be delivered in the same way reovirus is delivered. In fact, most of the oncolytic viruses were delivered by similar routes, particularly by intratumor injections. To Applicants' knowledge, no issue of predictability with respect to delivery methods has been raised in the prior art.

The Examiner appears to be specifically concerned about p53-expressing viruses, VSV, encephalitis virus, herpes zoster virus, hepatitis virus, influenza virus, varicella virus, and measles virus. Applicants wish to point out that the claims only encompass viruses that can selectively kill tumor cells, and these viruses are only injected into tumors that can be killed by the viruses (see claim 1). Therefore, no inoperable embodiments are encompassed by the claims. To expedite allowance, encephalitis virus, herpes zoster virus, hepatitis virus, influenza virus, varicella virus, and measles virus have been deleted from claim 7. p53-expressing viruses and VSV are known to selectively kill tumor cells (see, e.g., Bischoff J R. et al., "An Adenovirus Mutant that Replicates Selectively in p53-Deficient Human Tumor", Science 274(5286):373-6 (1996); Blagoslelonny, M. V., et al., "in vitro Evaluation of a p53-Expressing Adenovirus as an Anti-Cancer Drug", Int. J. Cancer 67(3):386-392 (1996); and Stojdl, D. F., et al., "Exploiting Tumor-Specific Defects in the Interferon Pathway with a Previously Unknown Oncolytic Virus", Nat. Med. 6(7):821-825 (2000)).

Working examples and guidance in the specification

The Office Action states that there are no examples indicating that reovirus has oncolytic effects on non-ras activated tumors. Since the claimed method involves injecting a virus to a tumor that can be killed by the virus, it is irrelevant whether reovirus can kill non-ras activated tumors.

The Office Action also states that there are no working examples or guidance indicating that a virus other than reovirus, such as the viruses included in claim 7, can be effective at reducing tumor growth when administered by the same routes as the reovirus. However, working examples are not required. Furthermore, since oncolytic viruses can generally be injected into a

tumor to kill the tumor cells, there is no reason to believe that the viruses cannot be injected into tumors according to the claimed invention to kill the tumor cells. In this regard, Applicants wish to remind the Examine that the USPTO bears the burden of establishing a *prima facie* case of non-enablement. It is incumbent upon the USPTO to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Bowen*, 181 USPQ 48, 51 (CCPA 1974). Here, the Office Action fails to provide any reason why non-reovirus cannot be delivered by the claimed method.

Quantity of experimentation

Since the claimed invention is a method of delivering oncolytic viruses, oncolytic viruses are well known in the art, the specification provides working examples for the delivery of reovirus, and it can be expected that other oncolytic viruses can be delivered in the same manner as reovirus, the required quantity of experimentation is low.

Level of the skill in the art

As stated in the Office Action, the level of the skill in the art is deemed to be high.

In conclusion, oncolytic viruses are known in the art, the claimed invention involves only tumors that can be killed by oncolytic viruses, and no evidence points to unpredictability. The specification provides representative working examples and guidance, and the quantity of required experimentation is low. Accordingly, a skilled artisan, deemed to have high skill levels, can practice the claimed invention without undue experimentation.

In view of the foregoing, withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. §102

The rejection of claims 1 and 7-13 under 35 U.S.C. §102 in view of Kooby *et al.* (FASEB Journal 13:1325-1334, 1999) is respectfully traversed for the reasons set forth below.

The standard of anticipation under 35 U.S.C. §102 is that each and every element of the claim must be found in the cited reference. *In re Marshall*, 198 USPQ 344 (CCPA 1978).

As discussed above, claim 1 is directed to a method for delivering a virus to a solid tumor to reduce growth of the tumor, comprising administering an effective amount of virus to a subject bearing the tumor, wherein the virus is capable of selectively killing cells of the tumor, by a base administration of injecting on the same day a composition comprising the virus into multiple sites inside the solid tumor, wherein the volume of the composition injected per site is between about 10% to about 100% of the volume of the tumor.

The Office Action states on page 7 (emphasis added),

> It is noted that the amended claim does not explicitly indicate that the composition comprising the virus is administered by multiple intratumoral injections, rather the claim is merely drawn to injecting on the same day a composition comprising the virus into multiple sites inside the tumor. As such, the claim encompasses administering the virus composition to multiple sites inside the tumor (on the same day) by injecting the composition into the tumor via a single injection that is not necessarily an intratumoral injection.

Applicants simply could not understand these statements. Why is "injecting into multiple sites inside the tumor" not necessarily an intratumoral injection? How can "injecting into multiple sites" be a single injection, unless the Examiner is referring to a single injection with a multi-injector device that results in multiple injections in one action? Clarification is respectfully requested.

In any event, the Examiner then argues that Kooby *et al.* teach a single injection, and that this single injection can be interpreted as injecting into multiple sites inside the solid tumor. This argument is unfounded. As pointed out in Applicants' last response, Kooby et al. teach a single injection of 50 μl of viral composition into a tumor of 50 mm^3, but not "injecting the viral composition into multiple sites into the tumor on the same day", as required in the claimed invention. Accordingly, Kooby et al. do not teach each and every element of the claimed invention, and the requirement of 35 U.S.C. §102 is not met.

Therefore, withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. §103

A. The rejection of claims 1-6 and 14-21 under 35 U.S.C. §103(a) over Kooby *et al.* (FASEB Journal 13:1325-1334, 1999) in view of Lee *et al.* (WO 99/08692) is respectfully traversed for the reasons set forth below.

To properly issue a rejection under 35 U.S.C. §103, the USPTO bears the initial burden to establish a prima facie case of obviousness by meeting three criteria. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings to arrive at the claimed invention. *In re Vaeck*, 20 USPQ 2d 1438 (Fed. Cir. 1991). Second, there must be a reasonable expectation of success. *Id.* Finally, the prior art reference or the combination of references must teach or suggest all the claim limitations. *In re Royka*, 180 USPQ 580 (CCPA 1974).

As discussed above, Kooby *et al.* do not teach each and every element of the claimed invention, particularly not the element of injecting the viral composition into multiple sites into the tumor on the same day. Lee et al. teach the use of reovirus in reducing tumor growth, but the reference does not specifically teach or suggest injecting the viral composition into multiple sites in the tumor on the same day. Since neither reference teach or suggest this element, combining the references does not cure the deficiency.

Accordingly, the combination of cited references do not teach or suggest all the claim elements, and the other two criteria under 35 U.S.C. §103 need not be discussed. Since the requirement under 35 U.S.C. §103 is not satisfied, withdrawal of this rejection is respectfully requested.

B. The rejection of claims 1, 8 and 9 under 35 U.S.C. §103(a) over Kooby *et al.* (FASEB Journal 13:1325-1334, 1999) in view of Barber *et al.* (U.S. Patent No. 5,662,896) is respectfully traversed for the reasons set forth below.

As discussed above, Kooby *et al.* do not teach each and every element of the claimed invention, particularly not the element of injecting the viral composition into multiple sites into the tumor on the same day. Barber *et al.* relate to methods for inhibiting tumor growth using recombinant viral vectors. The vector encodes an anti-tumor agent, such as an immune activator or a proliferation inhibitor. While Barber *et al.* teach that the viral vector may be injected several times in several different locations within the body of the tumor (column 11, lines 6-8 of Barber *et al.*), the reference does not teach or suggest delivery to multiple sites in a tumor on the same day. Since neither reference teach or suggest this element, the combination of the two references also does not teach or suggest this element.

Accordingly, the requirement under 35 U.S.C. §103 is not satisfied, and withdrawal of this rejection is respectfully requested.

C. The rejection of claims 1-21 under 35 U.S.C. §103(a) over Lee *et al.* (WO 99/08692) in view of Kooby *et al.* (FASEB Journal 13:1325-1334, 1999) is respectfully traversed for the same reasons as set forth in Section A, above. Briefly, Kooby *et al.* do not teach each and every element of the claimed invention, particularly not the element of injecting the viral composition into multiple sites into the tumor on the same day. Lee et al. teach the use of reovirus in reducing tumor growth, but the reference does not specifically teach or suggest multiple injections of the viral composition into the tumor on the same day. Therefore, the requirement under 35 U.S.C. §103 is not satisfied, and withdrawal of this rejection is respectfully requested.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement with Form PTO-1449 was filed in the above-captioned patent application on March 1, 2004. Applicants have not yet received the Examiner's copy of the Form PTO-1449, initialed to acknowledge the fact that the Examiner has considered the cited disclosed information.

It is respectfully requested that the Examiner initial and return a copy of the subject Form PTO-1449.

Conclusions

For the reasons set forth above, Applicants submit that the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's objections and rejections are hereby requested. Allowance of the claims remaining in this application is earnestly solicited.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at (650) 839-5044.

Enclosed is a $475.00 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: Sept. 23, 2004

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